Prostate cancer originating in basal cells progresses to adenocarcinoma propagated by luminal-like cells.

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Authors: Tanya Stoyanova, Aaron R Cooper, Justin M Drake, Xian Liu, Andrew J Armstrong, Kenneth J Pienta, Hong Zhang, Donald B Kohn, Jiaoti Huang, Owen N Witte, Andrew S Goldstein

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Public Summary:
In our manuscript “Prostate cancer originating in basal cells progresses to adenocarcinoma propagated by luminal-like cells" we address fundamental mechanisms of human cancer biology including whether different histological variants of cancer arise from a common or distinct target cells, and as tumors progress whether the cell-type of origin is continually required to maintain the disease. Tumor heterogeneity is a significant problem for clinical cancer treatment, as distinct variants of cancer respond differently to standard therapies. Our results provide functional evidence that a common basal cell of cancer origin can give rise to alternative variants of human prostate cancer. Since the cell-types driving cancer are important therapeutic targets, it is essential to determine whether the same cell population that initiates cancer is responsible for maintaining tumor progression. Our results indicate that cancer initiated in basal cells can evolve to adenocarcinoma maintained by luminal-like cells. These findings reveal that the cell of origin that initiates cancer is not continuously required to maintain and propagate the disease. Importantly, the cells responsible for initiating human prostate cancer can have a distinct cellular phenotype from the cells that maintain it. In this study we also generated highly relevant model of aggressive human prostate cancer that can be further used for preclinical testing in the near future.

Scientific Abstract:
The relationship between the cells that initiate cancer and the cancer stem-like cells that propagate tumors has been poorly defined. In a human prostate tissue transformation model, basal cells expressing the oncogenes Myc and myristoylated AKT can initiate heterogeneous tumors. Tumors contain features of acinar-type adenocarcinoma with elevated eIF4E-driven protein translation and squamous cell carcinoma marked by activated beta-catenin. Lentiviral integration site analysis revealed that alternative histological phenotypes can be clonally derived from a common cell of origin. In advanced disease, adenocarcinoma can be propagated by self-renewing tumor cells with an androgen receptor-low immature luminal phenotype in the absence of basal-like cells. These data indicate that advanced prostate adenocarcinoma initiated in basal cells can be maintained by luminal-like tumor-propagating cells. Determining the cells that maintain human prostate adenocarcinoma and the signaling pathways characterizing these tumor-propagating cells is critical for developing effective therapeutic strategies against this population.